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CLINICAL INVESTIGATION

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Treatment patterns and oncological outcomes of older adults with metastatic prostate cancer in real-world setting

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Abstract

Background: The landscape of systemic therapies for metastatic hormone-sensitive (mHSPC) and castration resistant prostate cancer (mCRPC) extensively improved within the last decades resulting in a significantly prolonged overall survival. However, subgroup analyses of phase III trials suggest potentially different overall survival outcomes for older adults.

Methods: We relied on our institutional metastatic prostate cancer database to identify mHSPC and subsequently mCRPC patients. Older adults were stratified according to age groups 70–74 versus ≥75–79 versus ≥80 years at metastatic occurrence. Subsequently, uni- and multivariable time to mCRPC and overall survival analyses were performed.

Results: Of 494 older adults, 217 (44%) were 70–74 versus 180 (36%) 75–79 versus 97 (20%) ≥80 years old. Rates of local prostate cancer treatment differed significantly between all three groups ($p < 0.01$). Regarding mHSPC treatment, androgen receptor signaling inhibitors (ARSI) were administered in 30–39% of patients and docetaxel with 9% in age group 70–74 years and 6% and 3% in age groups 75–79 years and ≥80 years. Regarding mCRPC treatment, significant differences between treatment proportions were observed ($p < 0.01$). Most common treatment was ARSI for all three groups. Conversely, chemotherapy was more frequently administered in patients aged 70–74 (16%), relative to 4% and 3% in 75-79 year and ≥80 year aged patients. In univariable and multivariable time to mCRPC analyses, overall survival in mHSPC and OS in mCRPC analyses, no significant differences between all three age groups were observed (all $p \geq 0.3$).

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Conclusions: Treatment patterns differ significantly between older adults with metastatic prostate cancer. However, these differences may not result in differences of overall life expectancy.

KEYWORDS

De novo; mCRPC; mCSPC, survival; metastatic prostate cancer; mHSPC

INTRODUCTION

The landscape of systemic treatment for metastatic prostate cancer has rapidly changed within the last two decades from androgen deprivation therapy (ADT) monotherapy to combination therapies with androgen receptor signaling inhibitor (ARSI) or chemotherapy or the combination of both for metastatic hormone-sensitive prostate cancer (mHSPC).[1,2] These combinations resulted in a substantial prolonged time until progression to castration resistant prostate cancer (mCRPC), as well as prolonged overall survival in phase III trials, as well as real-world settings.[3–7]

However, the field of mHSPC is currently undergoing another substantial change. Leaving the approach of classifying all mHSPC patients as one entity, clinicians and clinical trials tend to distinguish between low versus high volume mHSPC (according to CHAARTED criteria) or between primary De Novo versus secondary recurrent mHSPC.[6,8–12] Moreover, post-hoc analyses of phase III trials suggested that treatment outcomes in mHSPC patients also differ according to patient age of metastatic diagnosis. For example, in the ENZAMET and PEACE-1 trials, the effect of combination therapy compared with ADT alone, respectively the placebo arm, was slightly less pronounced in older adults with mHSPC.[13,14] Similar results were observed for the combination of apalutamide in the TITAN trial for ≥75 year old mHSPC patients.[15] Moreover, epidemiological data also suggested less overall survival benefit for radiation to the primary tumor in older adults with metastatic prostate cancer.[16] However, current real-world data regarding treatment patterns for mHSPC are scant. A recently published study by Fernando et al. explored differences in mCRPC treatments older adults with metastatic prostate cancer in Australia.[17]

We addressed the knowledge gap by relying on our institutional metastatic prostate cancer database to elaborate treatment patterns, as well as cancer-control outcomes such as time to mCRPC progression and overall survival in older adults with mHSPC. We hypothesized that differences in real-world settings exist between different age groups. Specifically, we hypothesized that in the oldest group of ≥80 years mHSPC patients, time to mCRPC or overall survival may be shorter, compared with younger mHSPC patients due to higher rates of comorbidities or proportions of frailty patients.

Key points

- Current patterns of older adults with metastatic prostate cancer indicate several important differences in mHSPC and mCRPC treatment patterns
- No differences in age group analyses have been observed in mHSPC patients
- Similarly, no differences in time to progression to mCRPC and survival in mCRPC have been observed

Why does this paper matter?

The landscape of systemic therapies for metastatic hormone-sensitive (mHSPC) and castration resistant prostate cancer (mCRPC) extensively improved within the last decades resulting in a significantly prolonged overall survival. The current study analyzed treatment patterns and oncological outcomes of 494 older adults aged ≥70 with metastatic prostate cancer and elaborated important differences in treatment patterns of mHSPC and mCRPC patients. However, these differences do not translate into differences in time to mCRPC or overall survival for both mHSPC and mCRPC patients.

METHODS

Study population

Upon obtaining approval from the local ethics committee (reference number: SUG-5-2018) and adhering to the principles of the Declaration of Helsinki, we retrospectively identified all patients with metastatic prostate cancer who were treated at the Department of Urology,

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University Hospital Frankfurt, Germany ($n = 1066$), and were discussed in the interdisciplinary tumor conference since the year 2014. Exclusion criteria consisted of patients aged <70 years at metastatic prostate cancer diagnosis. Inclusion criteria yielded 494 older adults with metastatic prostate cancer for analyses.

Statistical analysis

Descriptive statistics included analyzing the frequencies and proportions of categorical variables used in the study. Median values and interquartile ranges (IQR) were calculated for all continuously coded variables. Statistical significance for differences in proportions was evaluated using the Chi-square test, whereas differences in distributions were assessed using the *t*-test and Kruskal–Wallis test.

Age groups were categorized as either 70–74 versus 75–79 versus ≥80 years at metastatic prostate cancer diagnosis. For subsequent analyses in mHSPC setting, two different sets of analyses were applied. First, time to progression to mCRPC was calculated by Kaplan–Meier estimates and further analyzed in univariable, as well as multivariable Cox regression models. In multivariable Cox regression models' adjustment for unfavorable tumor and baseline characteristics was performed. Similar analyses were additionally conducted for overall survival in mHSPC setting. In the third part of the analyses, overall survival estimates between age groups were calculated in the setting of mCRPC.

All tests were two sided with a level of significance set at $p < 0.05$. R software environment for statistical computing and graphics (version 3.4.3) was used for all analyses.

RESULTS

Tumor and baseline characteristics

Of 494 eligible older adults with metastatic prostate cancer, 217 (44%) were 70–74 versus 180 (36%) 75–79 versus 97 (20%) ≥80 years old at diagnosis of metastatic disease (Table 1). Median follow-up was 27 months (IQR: 10–56 months). No differences were observed for median PSA at mHSPC diagnosis and its distribution, as well as PSA nadir under mHSPC treatment (both $p \geq 0.1$). Conversely, patients aged 70–74 years exhibited the highest rate of PSA decline ≥99% for mHSPC treatment (60%), versus 30% and 11% for patients aged 75–79 years and ≥80 years respectively ($p = 0.034$). Similar results were observed after stratification according to type of systematic treatment (Table 1).

Moreover, the rate of therapy lines for metastatic prostate cancer patients differed significantly between all three groups ($p = 0.018$). Additionally, rates of Eastern Cooperative Oncology Group (ECOG) ≥2 was lowest (3%) in patients aged 70–74 years, relative to age groups 75–79 years (8%) and ≥80 years (12%, both $p < 0.001$). Proportions of De Novo mHSPC, high volume, or high risk disease according to CHAARTED or LATITUDE criteria did not differ between the three compared age groups (all $p \geq 0.3$).[6,18]

Treatment patterns of older adults with metastatic prostate cancer

Rates of treatment to the primary prostate tumor differed significantly between all three aged groups (Table 1, $p < 0.01$). Specifically, rates of local therapy with either radical prostatectomy or radiation therapy was highest in age group 70–74 years (52%) versus 34% and 14% for respectively age groups 75–79 years and ≥80 years.

Regarding systemic treatment for mHSPC, no significant differences in proportions of treatment were observed ($p = 0.3$). ARSI administration rates ranged from 30 to 39% between all three groups. Rates of docetaxel chemotherapy were 9% in age group 70–74 years and 6% and 3% in age groups 75–79 years and ≥80 years. Conversely, all three groups harbored a high proportion of patients with ADT monotherapy for mHSPC, nmHSPC, or nmCRPC before progression to mCRPC (50–54%). This proportion of patients with ADT monotherapy decreased significantly within the last five years from 57% in 2018 to 28% in 2023.

Regarding systemic treatment for mCRPC, significant differences between treatment proportions were observed ($p < 0.01$). ARSI administration rates for all three groups were as follows: 30% versus 39% versus 34% for age groups 70–74 versus 75–79 versus ≥80 years. Conversely, chemotherapy with either docetaxel or cabazitaxel was more frequently administered in younger patients aged 70–74 years (16%), relative to 4% and 3% for age groups 75–79 years and ≥80 years respectively. Regarding sequential therapies, also significant differences were observed (Table 1, Figure 1). Overall, 61%, 15%, and 13% received two, three, or more than four therapy lines for metastatic prostate cancer disease, respectively.

Time to mCRPC progression

In time to mCRPC analyses (Figure 2), no significant differences between all three age groups were observed ($p = 0.1$). Specifically, median time to mCRPC was 14 versus 18 versus 20 months for age categories 70–74 years versus 75–79 years versus ≥80 years,

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TABLE 1 Patient and tumor characteristics of older adults with metastatic prostate cancer, stratified according to age at diagnosis.

Characteristic	70–74 yr $n = 217$ (44%)[a]	75–79 yr $n = 180$ (36%)[a]	≥80 yr $n = 97$ (20%)[a]	*p*-value[b]
Age at PCa diagnosis, years	70 (67, 72)	75 (70, 77)	80 (72, 82)	<0.001
Age at metastatic PCa diagnosis, years	72.2 (71.2, 73.6)	77.4 (76.2, 78.8)	82.6 (81.2, 84.2)	<0.001
PSA at mHSPC, ng/mL	48 (10, 411)	26 (9, 170)	39 (13, 133)	0.1
PSA Nadir at mHSPC, ng/mL	0.5 (0.1, 3.5)	1.2 (0.1, 5.8)	1.7 (0.3, 7.3)	0.6
PSA response ≥99%	34 (60)	17 (30)	6 (11)	0.034
PSA response ≥99%, ADT monotherapy mHSPC treatment	8 (40)	5 (25)	1 (11)	0.3
PSA response ≥99%, ARSI mHSPC treatment	16 (57)	7 (41)	5 (38)	0.4
PSA at mCRPC, ng/mL	23 (4, 82)	12 (6, 70)	25 (7, 82)	0.9
Systemic therapy lines	2.00 (2.00, 4.00)	2.00 (2.00, 3.00)	2.00 (2.00, 3.00)	0.018
ECOG ≥2	6 (3)	15 (8)	12 (12)	<0.001
Gleason 8–10	122 (56)	101 (56)	58 (60)	0.5
Local therapy RP/RT	103 (52)	67 (34)	28 (14)	<0.01
High volume mHSPC	70 (32)	45 (25)	31 (32)	0.6
High risk mHSPC	69 (32)	49 (27)	31 (32)	0.9
De Novo mHSPC	111 (51)	97 (54)	47 (49)	0.7
Treatment mHSPC				0.3
ARSI	68 (31)	53 (29)	36 (37)	
Docetaxel	19 (9)	11 (6)	3 (3)	
Triplet	5 (2)	4 (2)	0 (0)	
Other	2 (1)	5 (3)	1 (1)	
ADT (nmHSPC/mHSPC/nmCRPC)	114 (52)	100 (57)	54 (54)	
Treatment mCRPC				<0.01
ADT mono	14 (6)	11 (6)	5 (5)	
ARSI	64 (30)	71 (41)	33 (34)	
Chemotherapy	34 (15)	8 (4)	3 (3)	
Lu-PSMA	6 (3)	7 (4)	6 (6)	
Radium	5 (2)	4 (2)	1 (1)	
Sequence mHSPC-mCRPC				0.02
ADT- > ADT	14 (7)	11 (6)	5 (5)	
ADT- > Chemo	18 (8)	4 (2)	2 (2)	
ADT- > ARSI	41 (19)	52 (29)	23 (24)	
Chemo- > Chemo	1 (0.5)	0 (0)	0 (0)	
Chemo- > ARSI	10 (5)	6 (3)	3 (3)	
ARSI- > Chemo	15 (7)	4 (2)	1 (1)	
ARSI- > ARSI	9 (4)	13 (7)	6 (6)	

Abbreviations: ADT, Androgen deprivation therapy; ARSI, Androgen receptor signaling inhibitor; Chemo, Chemotherapy; ECOG, Eastern Cooperative Oncology Group; mCRPC, metastatic castration resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; NA, Not available; nmHSPC, non-metastatic HSPC; PCa, Prostate cancer; Yr, year.

[a]Median (IQR); *n* (%).

[b]Kruskal–Wallis rank sum test; Pearson's Chi-square test; Fisher's exact test.

respectively. One-year mCRPC-free rates were 60% versus 65% versus 72% for age groups 70–74 years versus 75–79 years versus ≥80 years. In univariable Cox regression models, as well as after additional multivariable adjustment (Supplemental Table 1A), increased age did not predict lower time to mCRPC (all $p \geq 0.05$).

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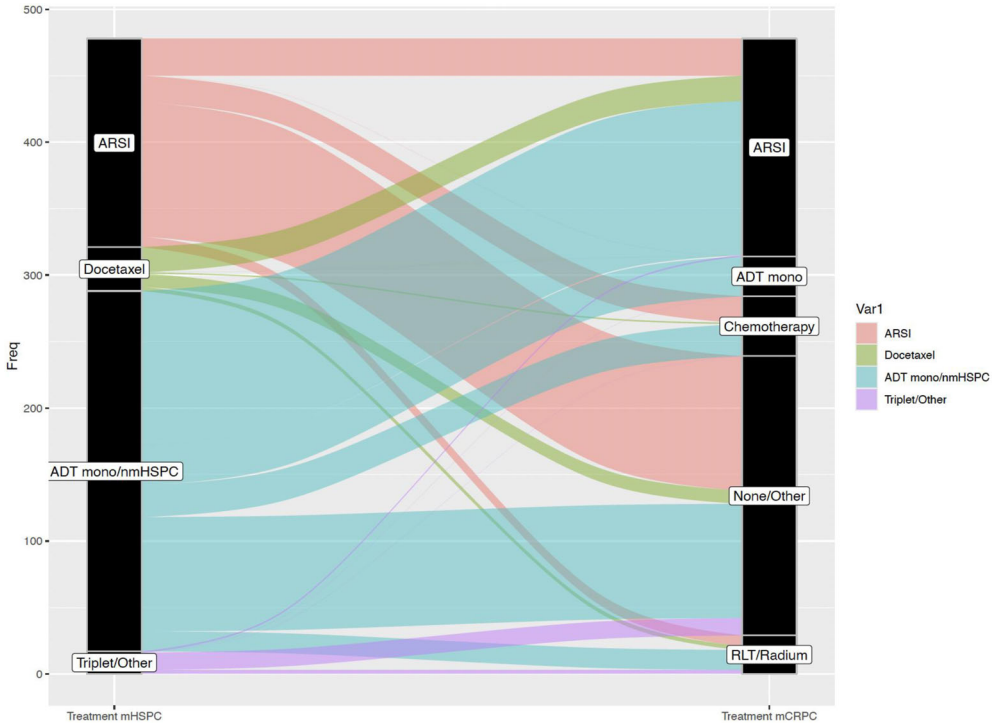


FIGURE 1 Sankey plot depicting treatment changes of older adults with metastatic prostate cancer in hormone-sensitive (mHSPC) and castration-resistant (mCRPC) setting. ADT, Androgen deprivation therapy; ARSI, Androgen receptor signaling inhibitor.

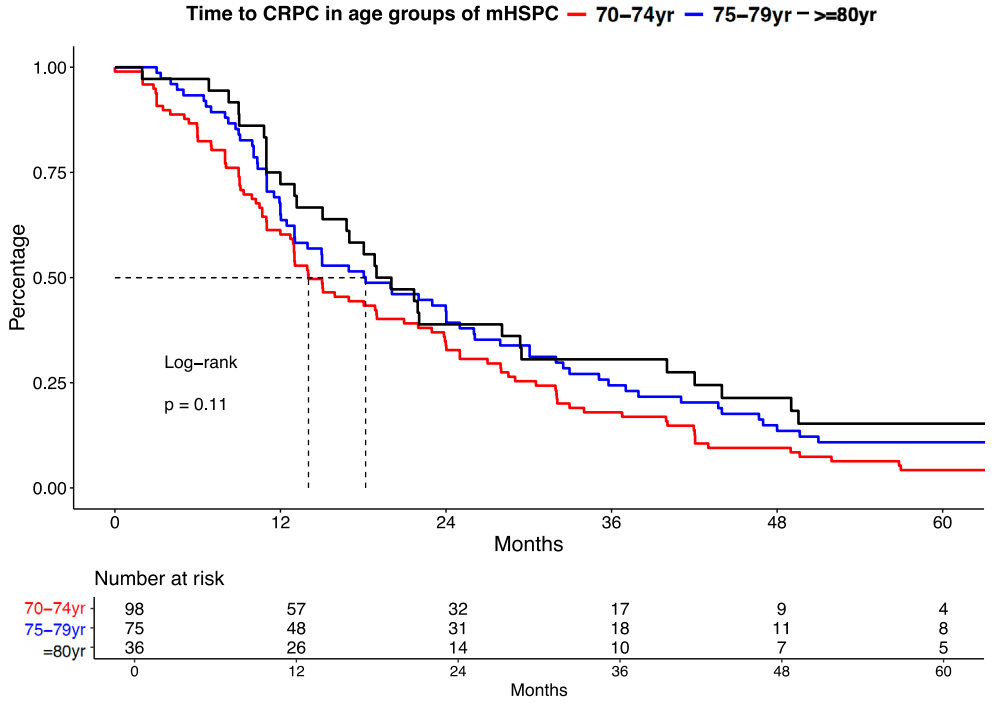


FIGURE 2 Depicting overall survival in older adults with metastatic hormone-sensitive prostate cancer (mHSPC), stratified according to age at diagnosis. yr: Years.

Overall survival of older mHSPC adults

In overall survival analyses of older mHSPC adults (Figure 3), no significant differences between all three age groups were observed ($p = 0.5$). Specifically, median overall survival was 76 versus 64 versus 60 months for age categories 70–74 versus 75–79 versus ≥80 years, respectively. Three-year overall survival rates were 74% versus 72% versus 64% for age groups 70–74 versus 75–79 versus ≥80 years. In univariable Cox regression models, as well as after additional multivariable adjustment (Supplemental Table 1B), increased age was not associated with shorter OS (all $p \geq 0.4$).

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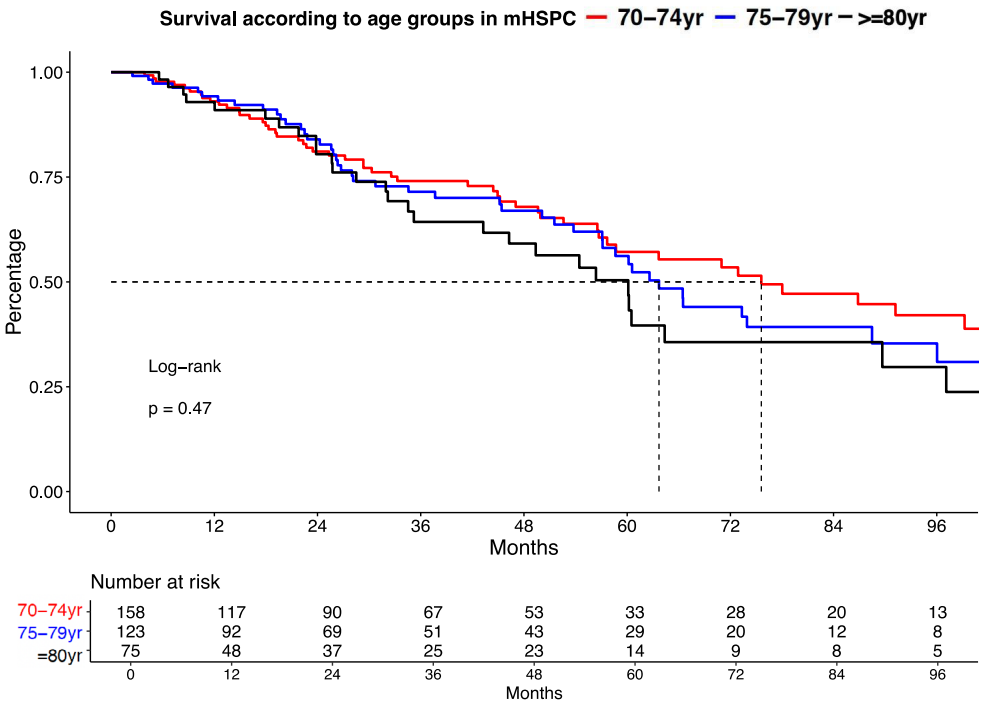


FIGURE 3 Depicting time to castration resistant prostate cancer (CRPC) in older adults with metastatic hormone-sensitive prostate cancer (mHSPC), stratified according to age at diagnosis. yr: Years.

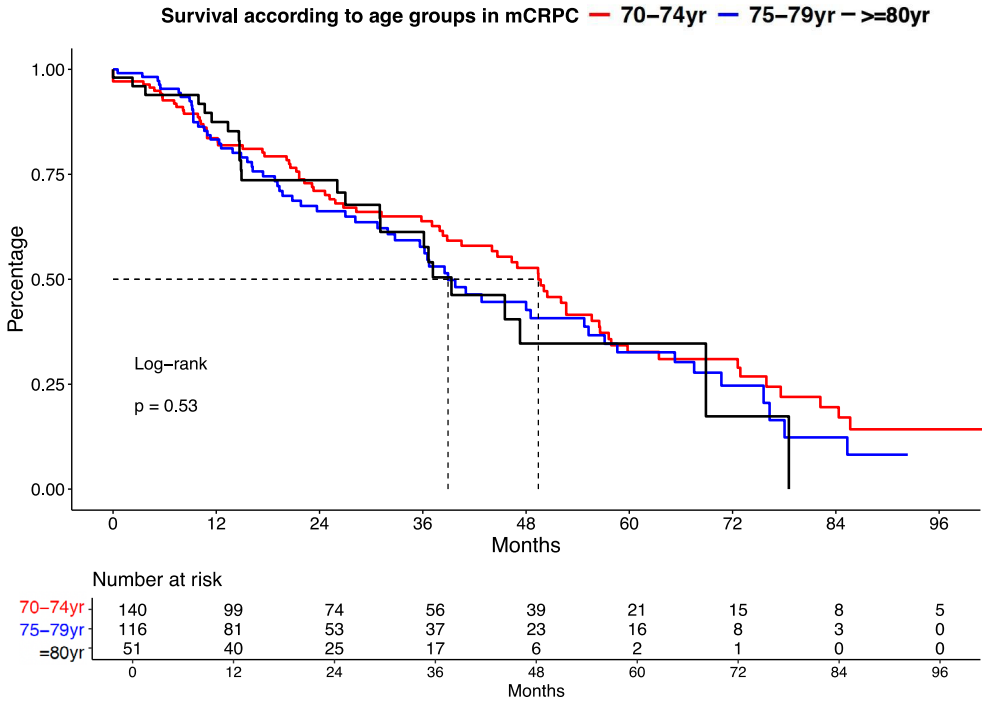


FIGURE 4 Depicting overall survival in older adults with metastatic castration resistant prostate cancer (mCRPC) patients, stratified according to age at diagnosis. yr: Years.

Overall survival of older mCRPC adults

In overall survival analyses of older mCRPC adults (Figure 4), also no significant differences between all three age groups were observed ($p = 0.5$). Specifically, median overall survival was 49 versus 39 versus 39 months for age categories 70–74 versus 75–79 versus ≥80 years, respectively. Three-year overall survival rates were 64% versus 58% versus 61% for age groups 70–74 years versus 75–79 years versus ≥80 years. In univariable Cox regression models, as well as after additional multivariable adjustment (Supplemental Table 1C), increased age did also not predict worse overall survival of mCRPC patients (all $p \geq 0.2$).

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DISCUSSION

We hypothesized that important baseline and tumor characteristics differences in real-world settings exist between different age groups of older adults with metastatic prostate cancer. Moreover, we also hypothesized that differences in treatment patterns of older mHSPC and mCRPC adults exist and that these differences may translate into different cancer-control outcomes. We tested these hypotheses with our institutional metastatic prostate cancer database and made several noteworthy observations.

First, we observed that 20% of all older adults with newly diagnosed and treated metastatic prostate cancer above 70 years are aged ≥80 years. This proportion is interestingly high and emphasized the need of geriatric assessment and multidisciplinary treatment approaches. However, no differences regarding most baseline characteristics existed between all compared age groups.[19,20] Specifically, rates of high risk or high volume metastatic disease did not differ between all age groups. Similarly, rates of De Novo versus secondary recurrent metastatic disease did not differ between all three age groups. These rates are of interest because one may have expected that high volume or high risk mHSPC rates may increase with age due to in general higher Gleason score proportions in this age categories and worse cancer characteristics.[21,22]

Second, we observed that differences in treatment patterns exist in older adults with metastatic prostate cancer. Unsurprisingly, the rate of local therapy to the primary prostate cancer decreased with age. This observation may be attributable to the fact that the primary prostate cancer diagnosis was also diagnosed at increased age of these patients, and no local therapy was recommended in those men. However, generally speaking, a trend toward higher proportions of local treatment with external beam radiation therapy for low volume mHSPC patients was recently observed by Stolzenbach et al.[23]

In mHSPC setting, proportions of systematic treatment did not differ between all three compared age groups. Highest rates of combination therapy were ARSI administration with almost similar rates between all compared groups. Conversely, rates of chemotherapy decreased with increase age from 16% (70–74 years) to 3% (≥80 years) and may be explained by higher proportions of ECOG ≥2 patients in the oldest age group and the possible lethal side effects in frail patients.[24] However, a high proportion of all age groups patients received ADT monotherapy or were nmHSPC or nmCRPC patients before progressing to mCRPC. Because those patients (ADT monotherapy for mHSPC, nmHSPC, or nmCRPC before progressing to mCRPC) could not be distinguished, these limitation needs to be considered in the interpretation of the current data. However, in sensitivity analyses a trend toward combination therapies and less ADT monotherapy within the last years could be observed.

In setting of mCRPC, ARSI was the most frequent administered systemic therapy. Moreover, younger patients received significantly more systemic therapy lines than older adults. These observations are in an agreement with previous published studies. For example, an Australian real-world cohort of 753 mCRPC patients explored also [1]more therapy lines for younger mCRPC patients. However, rates of ARSI administration increased significantly with advanced age in this report and was 84% in patients aged >85 years.[17] These observations indicate the role for ARSI in older adults, because side effects may be less severe than with chemotherapy.[25] However, proportions of ARSI administration seem to differ according to geographical region due to differences in healthcare systems and reimbursements.[26] Nonetheless, rates of systemic treatments in mCRPC remain low in general. For example, a recently published report showed that 22% of mCRPC patients do not receive life-prolonging systemic treatment.[27]

Third, in cancer-control outcome comparisons, we did not observe significant differences regarding time to mCRPC, overall survival of mHSPC or overall survival of mCRPC patients between the three compared age groups 70–74 versus 75–79 versus ≥80 years. Similar results were also observed in the Australian mCRPC cohort, in which no differences in overall survival of mCRPC patients were observed between different older adults age groups.[17] These real-world setting observations are of note because they reflect clinicians' choices of systemic treatments and sequential therapies for different population groups. These observations are also important because differences in systemic treatments have been observed, but not translated into cancer-control outcomes.

In general, outcomes of metastatic, and especially older adults with metastatic prostate cancer have increased significantly over the past decades.[28,29] Due to this extended life expectancy in general population and in localized prostate cancer patients due to better medical facilities and treatments, clinicians need to adjust their treatment carefully in older adults with mHSPC or mCRPC to avoid undertreatment of patients in advanced age categories, especially in times of demographic changes.[30,31] In conclusion, our data suggest proper treatment selection for each age category because overall survival did not differ between all analyzed three age groups, which could be interpreted as a sufficient balance between treatment-related mortality and mortality due to undertreatment in patients with possibly high rates of comorbidities or frailty.

Due to the retrospective single-center design of our study, limitations should be acknowledged. Firstly, the results may be influenced by potential selection bias

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inherent in retrospective analyses, as well as by the specific characteristics of our patient cohort, which may not be representative of all populations and geographical regions. Additionally, the reliance on data obtained from medical records raises the possibility of incomplete or inaccurate documentation, which could impact the validity and reliability of our findings. Furthermore, the observational nature of the study or lack of sample size in subgroup analyses may limited our ability to establish causal relationships between variables, and residual confounding factors may exist despite our efforts to adjust for known covariates. Therefore, although our study provides valuable insights, caution is warranted when interpreting and generalizing the results to other settings or populations.

Taken together, the current study analyzing treatment patterns and oncological outcomes of older adults with metastatic prostate cancer indicates despite several important differences in treatment patterns of mHSPC and mCRPC patients that no differences in time to mCRPC or overall survival exist.

AUTHOR CONTRIBUTIONS

Project development, Data collection, Data analysis, Manuscript writing: M Wenzel. Project development, Data collection, Data analysis: B Hoeh. Project development, Data collection, Data analysis: N Wagner. Project development, Data collection, Data analysis: F Koll. Data collection, Manuscript editing: C Siech. Manuscript editing, Supervision: C Humke. Manuscript editing, Supervision, Validation: T Steuber. Manuscript editing, Supervision, Validation: M Graefen. Manuscript editing, Supervision, Validation: D Tiilki. Manuscript editing, Supervision, Validation: L Kluth. Data collection, Manuscript editing: M Traumann. Manuscript editing, Supervision, Validation: S Banek. Manuscript editing, Supervision, Validation: FKH Chun. Project development, Manuscript writing. Supervision: P Mandel.

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CONFLICT OF INTEREST STATEMENT

The aurthors declare no potential conflicts of interest.

FINANCIAL DISCLOSURE

The authors declare no funding for the current study.

SPONSOR'S ROLE

None.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

Supplemental Table 1. Univariable and multivariable Cox regression models predicting overall survival (OS) and time to castration resistant prostate cancer (mCRPC) according to age groups.

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